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24 March 2019

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Dear Chief Police Officer Johnson

Re: No scientific evidential support for pill testing

I write as the President of Drug Free Australia, as the former Chairman of Prime Minister Howard's Australian National Council on Drugs (ANCD) during the Tough on Drugs era which saw Australian drug use reduced by 39% between 1998 and 2007, and as a previous Australian representative on the United Nations' International Narcotics Control Board (INCB).

Drug Free Australia seeks to inform you, as the ACT Chief Police Officer, of the scientific evidence on MDMA-related deaths in this country as it relates to the current push for pill testing at music festivals.

Key to our observations is the only academic journal study of 82 Australian MDMA related deaths from 2001-2005 (Attachment 4). We can summarise the current science as follows.

Harm Reduction Australia, which has been the country's chief advocate for pill testing, has given the public three spurious rationales for the urgent implementation of pill testing.

1. **Possible deaths from dangerous impurities -** Drug Free Australia has found no reported deaths in Australia from 'impurities' in ecstasy pills
2. **Deaths from high purity causing overdoses** – medical literature indicates that actual overdoses from MDMA are rare (see Attachment 2). Drug Free Australia also notes that logic demands that purity, in and of itself, cannot empirically be a major hazard because any large batch of high purity pills will be consumed by a high number of consumers, where a good percentage would be expected to be, if Harm Reduction Australia was correct, hospitalised or deceased. But mass hospitalisations or deaths from high purity batches are not happening in Australia
3. **Deaths from unknown other drugs cut with MDMA** – Drug Free Australia has identified three deaths in Melbourne in January 2017 from unknown other drugs cut with MDMA (see

Attachment 3), seven PMA deaths from 1995 to 2007 and a Gold Coast NBOMe fatality, indicating there are few deaths in Australia from this threat. Conversely there are literally **hundreds** of Australian deaths from the very thing which pill testing tacitly approves – normal recreational doses of MDMA

Nullifying all such rationales for pill testing are the following overwhelming facts.

1. The only Australian journal study of 82 MDMA-related deaths from 2001-2005 shows that it is **MDMA itself that is responsible for almost every ecstasy pill death** within Australia and **deaths are from normal recreational doses of MDMA** (see Attachment 4). We have had literally hundreds of MDMA deaths – not from impurities, not from overdoses, but from MDMA itself. NSW Health Minister Brad Hazzard confirmed in the 22 January 2019 edition of the Daily Telegraph that ecstasy was implicated in each of the 5 NSW festival deaths this summer. *The Canberra STA-SAFE pill testing trial, despite their mandatory legal disclaimers about no drug being completely safe,* ***greenlighted the very cause of most Australia deaths****, that is, normal recreational doses of MDMA (see Attachment 1 for definition of 'normal recreational doses') (see also Attachment 8 for the trial advocates' expressed views on the greater 'safety' their trial would offer)*
2. The aforementioned Australian study shows that MDMA used in a polydrug use setting was responsible for most of the 82 deaths (59% - see Attachment 4)**, however pill testing cannot test for polydrug use**
3. The existing evidence base shows that many die of an individual allergic-like reaction to MDMA (MDMA was the sole cause of death for 23% of decedents in the study of 82 deaths mentioned above - see Attachment 4), **however pill testing cannot test for individual reactions**
4. The same study indicates **most Australian MDMA deaths occur at home** (62% in fact - see Attachment 4), not at festivals, raves or nightclubs where 15% took a fatal dose of ecstasy. Pill testing does not address the vast majority of Australian MDMA deaths
5. The Canberra pill testing trial's equipment – a Bruker Alpha II **may not be capable of detecting other dangerous drugs cut with MDMA** where there are three, four or more adulterants in the pills or caps (see Attachment 5). The same equipment may also not be capable of detecting most of the fast-evolving other substances that could potentially be used in ecstasy pills in the future (see Attachment 6)
6. The Canberra STA-SAFE trial's Bruker Alpha II **could not determine with any accuracy the main substance in 53% of the pills tested** according to their own Evaluation of the trial(see Attachment 7) making it of limited use due to the uncertainty
7. The existing evidence base indicates that **a scraping from a pill cannot guarantee that it is representative** of what is in the pill, providing no certainty with non-pharmaceutical quality pills and caps (see Attachment 6)
8. The required police amnesty for festival drug users demanded by pill testing removes certain crucial impediments to drug use. The Australian National Drug Strategy Household Survey for 2016 reported that 31.1% of the 25,000 respondents said that they would not take drugs 'for reasons related to the law', and 18.1% said they did not take drugs 'for fear of death'. Government-funded pill testing arguably **gives the appearance of some level of government sanction for MDMA use** which removes the clear appearance of illegality, while the **spurious safety** that has been strongly promoted by pill testing advocates (see Attachment 8) **removes much of the concern regarding fear of death for the latter 18%**
9. Harm Reduction Australia, which is behind the pill testing misinformation, is also pushing for the legalisation of cannabis (see Attachment 9), which seeks only to save drug users from the negative consequences of the law and NOT from the numerous harms cannabis causes to the individual user and the community. The drug normalisation overtones of the current pill

testing misinformation linked with the concurrent push for cannabis legalisation **raises the valid question as to whether the pill testing push could possibly be motivated by a further normalising of drug use towards a drug legalisation outcome** , coopting the ACT Government and Police towards that end

10. Despite many claims to the contrary, there are **no studies from Europe demonstrating that pill testing saves lives.** The only science from Europe uses notoriously unreliable self-reported changes in drug use behaviours by the drug users themselves, with no studies attempting to quantify lives saved by pill testing

In summary, pill testing advocates have previously treated normal recreational doses of MDMA as relatively safe, when they are not. Pill testing's requirement of a police amnesty for drug users is based on a campaign of unfounded misinformation not backed by science.

I would urge you, as the ACT Chief Police Officer, to ask a number of your forensics and medical personnel to review our documentation to confirm our deep concerns. We will also take up our concerns with the Chief Minister because in Drug Free Australia's view, the drug normalisation of pill testing only serves to create uncertainty around our Australian Territory and Federal laws, making the work of policing so much more difficult. Drug Free Australia's Research Director, Gary Christian, is available to travel to Canberra to answer any questions you may have regarding this letter or attachments.

We would be very keen to hear further from you.

Yours sincerely

Major Brian Watters AO
President, Drug Free Australia
Chairman, Prime Minister's Australian National Council on Drugs (ANCD) 1998-2005
Australia's representative to the United Nations International Narcotics Control Board (INCB) 2004-2012

ATTACHMENT 1

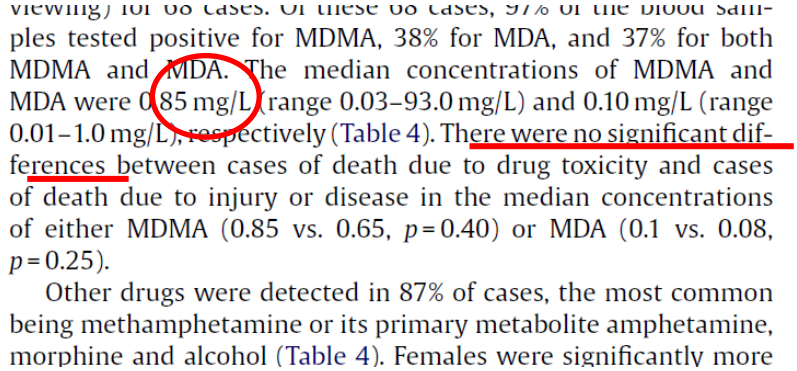
Normal recreational doses of MDMA causing most deaths

Dr David Caldicott has recently tried to downplay the fact that most Australian MDMA deaths are from **normal recreational doses of MDMA**, which are usually 100-150mg per pill or cap (Disposition of Toxic Drugs and Chemicals in Man, ed. Ranald Baselt 9th ed 2011 p 1078).

We have previously cited in this letter the single Australian journal study on MDMA-related deaths https://www.ncbi.nlm.nih.gov/pubmed/19604654 (see Attachment 4) which found that of 82 Coroners' reports between 2001 and 2005 analysed by the researchers, MDMA was the sole drug causing death in 23% of the cases, while 59% of deaths were from MDMA used in a polydrug use setting. The remaining 18% were deaths due to suicide, accidents etc where MDMA was present.

Notably, this Australian study found that,

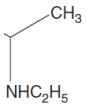
> "There were no significant differences between cases of death due to drug toxicity and cases of death due to injury or disease in the median concentrations of either MDMA (0.85 vs. 0.65, p 0.65, *p*=0.40) or MDA (0.1 vs. 0.0, *p*=0.25)."



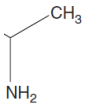
viewing) for 68 cases. Of these 68 cases, 97% of the blood samples tested positive for MDMA, 38% for MDA, and 37% for both MDMA and MDA. The median concentrations of MDMA and MDA were 0.85 mg/L (range 0.03–93.0 mg/L) and 0.10 mg/L (range 0.01–1.0 mg/L), respectively (Table 4). There were no significant differences between cases of death due to drug toxicity and cases of death due to injury or disease in the median concentrations of either MDMA (0.85 vs. 0.65, $p = 0.40$) or MDA (0.1 vs. 0.08, $p = 0.25$).

Other drugs were detected in 87% of cases, the most common being methamphetamine or its primary metabolite amphetamine, morphine and alcohol (Table 4). Females were significantly more

We note that the **median average** 0.85 mg per litre falls well within the range of observed MDMA deaths ranging from 0.1mg/litre to 2.4 mg/litre http://bja.oxfordjournals.org/content/96/6/678.full, (see Attachment 10) where it can be said with **absolute certainty** that 50% of the 67 Australian deaths caused by MDMA toxicity during those years were normal recreational doses (ingestion of 1.5mg of MDMA per kilogram body weight and the associated blood levels are considered moderate. https://thedea.org/mdma-risks-science-and-statistics-technical-faq/).



MDEA



MDA

Serotonin (5-HT)

the significance of which is not known.[68] MDMA has a plasma half-life of 7.6 h. Typically, after oral ingestion (75–150 mg), desired effects begin within 1 h and last 4–6 h.[68] Blood levels in asymptomatic users and those with serious side-effects are often similar, suggesting that adverse reactions are likely to relate to the circumstances in which the drug is taken, and that there may also be an idiosyncratic component.[28] A number of fatalities have been reported with blood levels of 0.1–2.1 mg litre^{-1}.[31] However, a case of a deliberate overdose of MDMA in which the blood level reached 4.3 mg litre^{-1} with no more than mild sinus tachycardia and a degree of somnolence has been reported.[54] Another analytically documented overdose resulted in a plasma MDMA of 7.72 mg litre^{-1}, the highest recorded in a surviving patient, with just a 'hangover', tachycardia and hypertension.[31] The highest level reported in association with multi-organ failure in a subsequent survivor was 7 mg litre^{-1}.[6]

MDMA metabolism involves two main pathways. In one, *O*-demethylenation is followed by catechol-

Given that the BJA study records blood concentrations in users who have survived with 7.7 mg/l, which is so much higher than typical levels in decedents, and given that MDMA overdoses are rare (noting that there was a suicide in this study with a staggering 93 mg/l), Drug Free Australia's conclusion is that there is every good reason to believe that most Australian MDMA deaths are from normal recreational doses of MDMA.

ATTACHMENT 2

Ecstasy overdoses are rare

Pill testing Dancesafe USA says "Stop calling them overdoses"

The pill testing advocate, Dancesafe, in the USA insists that overdoses are rare.

They say at https://dancesafe.org/mdma-related-deaths-stop-calling-them-overdoses/:

> One of the most prolific—and most dangerous—pieces of media misinformation is the claim that MDMA-related deaths are the result of overdoses. This is not true, and this dangerous myth will be explained in a moment. First, however, it is important to understand what the word "overdose" actually means.
>
> Overdosing means taking a higher than appropriate dose of a medicine or a drug. In other words, it simply means *taking too much* or taking a "dose" that is "over" the proper therapeutic or recreational amount. The association of the word "overdose" with "drug-related death" is primarily reflective of heroin and opiate-related deaths, where the majority of fatalities may, in fact, result of overdosing. However, MDMA-related deaths are rarely the result of an overdose, and calling them overdoses is dangerous and negligent. It sends the message that "you will be okay as long as you don't take too much," which is simply not true. *In the vast majority of cases of MDMA-related deaths, where no other drugs were found in the person's bloodstream, the deceased had taken a dose within the normal range for appropriate therapeutic or recreational use.*

Mothership Drug Policy Alliance says MDMA overdoses are rare

The Soros-funded Drug Policy Alliance, which seeks the legalisation of illicit drugs and which is the virtual mothership to all drug liberalisation or legalisation organisations worldwide takes the factual stance that MDMA overdoses are rare.

> Most of MDMA's potential harms derive from the setting of its use.14 Although few adverse effects have been reported, hyperthermia – a dangerously high increase in body temperature – is the most common problem related to ecstasy. Hyperthermic reactions
>
> result from physical exertion (such as dancing) in an overheated environment without replenishing fluids,15 which is why users take breaks and consume fluids like water or Gatorade.16 *Overdoses are extremely rare* (our emphasis) and are also usually linked to dehydration or mixing drugs, rather than as a

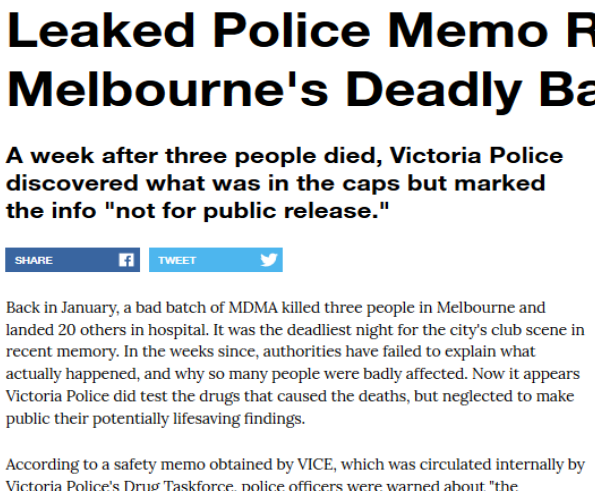
direct result of using ecstasy.
https://www.drugpolicy.org/sites/default/files/DPA_Fact_Sheet_MDMA.PDF

ATTACHMENT 3

Deaths from unknown other drugs

Three deaths in Melbourne in 2016

There were three deaths in Melbourne in January 2017 from other drugs cut with MDMA in purported ecstasy caps. See Vice article at: https://www.vice.com/en_au/article/3dp5pk/leaked-police-memo-reveals-what-was-in-melbournes-deadly-batch-of-mdma



Leaked Police Memo Reveals What Was in Melbourne's Deadly Batch of MDMA

A week after three people died, Victoria Police discovered what was in the caps but marked the info "not for public release."

SHARE TWEET

Back in January, a bad batch of MDMA killed three people in Melbourne and landed 20 others in hospital. It was the deadliest night for the city's club scene in recent memory. In the weeks since, authorities have failed to explain what actually happened, and why so many people were badly affected. Now it appears Victoria Police did test the drugs that caused the deaths, but neglected to make public their potentially lifesaving findings.

According to a safety memo obtained by VICE, which was circulated internally by Victoria Police's Drug Taskforce, police officers were warned about "the

The article had the following to say:

> "The reason why [an MDMA cap containing] NBOMe is so dangerous is that if you do a reagent test, even if you're really careful about it, it'll tell you it's just MDMA," says Will Tregoning, the executive director of Unharm. Additionally, he says it's unusual that NBOMe was being sold as MDMA at all, especially in an international context.
>
> After the Chapel Street deaths, Dr Monica Barratt from the National Drug and Alcohol Research Centre (NDARC) arranged for a sample of the bad batch to be sent to Energy Lab in Barcelona for testing. She explains they found the same ingredients as Victoria Police. "The tests we've done in Spain last week match what we now know that the police already knew, which is that the capsules contained 25C-NBOMe and 4-FA," Dr Barratt says. "You've got pretty strong circumstantial evidence, although it's impossible for us to say that it's exactly the same."
>
> On the forum Bluelight, Dr Barratt warned users about the small amount of MDMA found in the caps. "This may be an indication that the manufacturers

were hoping to fool reagent test kits by including enough MDMA to produce a positive result," **she wrote**. Essentially, to pick up the 4-FA and 25C-NBOMe, you would've needed equipment like an Alpha Bruker and gas chromatography mass spectrometry (GC/MS)—both of which Victoria Police have in their laboratories.

7 PMA deaths from 1995 to 2007

https://www.smh.com.au/national/pma-found-in-drugs-haul-20071011-gdrbhj.html

Gold Coast NBOMe death

https://www.news.com.au/national/queensland/crime/drug-nbomb-that-caused-gc-overdoses-was-the-same-drug-that-killed-backpacker-rye-hunt/news-story/be610a069b46c5b92d9a5d3e4879c32f

ATTACHMENT 4

Australian study of 82 MDMA-related deaths (2001-2005)

Following is the pdf of the Australian study on MDMA-related deaths

Drug and Alcohol Dependence 104 (2009) 254–261

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Methylenedioxymethamphetamine (MDMA)-related fatalities in Australia: Demographics, circumstances, toxicology and major organ pathology

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ARTICLE INFO

Article history:
Received 2 December 2008
Received in revised form 12 May 2009
Accepted 13 May 2009
Available online 14 July 2009

Keywords:
MDMA
Ecstasy
Fatalities
Death
Cardiovascular
Pathology

ABSTRACT

Aim: To examine the demographic characteristics, circumstances, toxicology and major organ pathology of MDMA-related deaths in Australia.
Methods: Retrospective review of cases in which MDMA was a cause of death, as identified from the National Coronial Information System.
Results: 82 cases over a 5-year period were identified. The majority of decedents were male (83%), with a median age of 26 years. Deaths were predominantly due to drug toxicity (82%), with MDMA the sole drug causing death in 23% of cases, and combined drug toxicity in 59% of cases. The remaining deaths (18%) were primarily due to pathological events/disease or injury, with MDMA a significant contributing condition. Cardiovascular pathology, typically atherosclerosis, was detected in 58% of decedents, with moderate–severe atherosclerosis in 23% of cases. The prevalence of such pathology is higher than that expected among similarly aged members of the general population. Cerebrovascular pathology, primarily cerebral haemorrhage and hypoxic damage, was present in 12% of cases.
Conclusions: MDMA has contributed to a clinically significant number of deaths in Australia. The prevalence of cardiovascular pathology was similar to that among methamphetamine and cocaine fatalities. Whilst cardiovascular pathology may reflect the use of other stimulants, the cardiotoxic properties of MDMA have been well-documented. Future studies examining MDMA-related morbidity and mortality in the context of other risk factors are recommended. Overall, the current study highlights the need to educate users about the potential harms of MDMA use, particularly that in conjunction with other stimulants, opioids and alcohol, which are known to increase overall toxicity.

1. Introduction

MDMA (3,4-methylenedioxymethamphetamine, "ecstasy"), is an amphetamine derivative, with hallucinogenic and stimulant properties. The popularity of MDMA has increased since the late 1980s, when its use became a feature of the underground dance or "rave" scene (Gill et al., 2002). In Australia, MDMA is the second most widely used illicit drug after cannabis. According to the 2007 National Drug Strategy Household Survey data, 8.9% (1.5 million) of the general population reported lifetime use of MDMA, with 3.5% (0.6 million) reporting use in the preceding 12 months (Australian Institute of Health and Welfare, 2008). Use is most prevalent among 20–29-year-old males, who were more likely to report lifetime (25.7%) and recent (13.8%) use of MDMA.

As the use of MDMA has increased, reports of associated adverse consequences have become more frequent (Burgess et al., 2000). Acute adverse physical effects reported by users include jaw clenching, tooth grinding (bruxism), blurred vision, palpitations, headache, nausea, and increased body temperature (Topp et al., 1999; Kalant, 2001; Gowing et al., 2002; Liechti et al., 2005; Baylen and Rosenberg, 2006). The most widely reported acute psychological effects are anxiety, depression and paranoia (Topp et al., 1999; Baylen and Rosenberg, 2006).

Emergency department and mortality data, in addition to users' reports, suggest that serious complications of MDMA use are less common than those associated with opioids, cocaine, or methamphetamine and, relative to the prevalence of use, are not commonplace (Gowing et al., 2002; Liechti et al., 2005; Darke et al., 2007). Nevertheless, acute toxicity following MDMA use can, and does, occur. Hyperthermia is one of the most widely reported toxic reactions to MDMA and a common finding among MDMA-related fatalities (Kalant, 2001; Gowing et al., 2002; Patel et al., 2005a,b; Darke et al., 2007). Hyperthermia can cause life-threatening complications such as seizures, rhabdomyolysis, acute renal failure, disseminated intravascular coagulation, and severe liver toxicity and failure (Milroy et al., 1996; Kalant, 2001; Gowing et al., 2002;

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doi:10.1016/j.drugalcdep.2009.05.016

Darke et al., 2007). Whilst liver toxicity is often secondary to hyperthermia, it can also occur in the absence of hyperthermia (Milroy et al., 1996; Burgess et al., 2000; Gowing et al., 2002; Darke et al., 2007). In response to increases in body temperature, perspiration, and thirst, induced by MDMA itself, ambient temperature and/or physical activity, users often increase fluid intake. The over-consumption of water can cause dangerous sodium and water imbalances, leading to hyponatraemia, commonly referred to as "water intoxication". Hyponatraemia can cause confusion and reduced consciousness and may induce cerebral oedema (Gowing et al., 2002; Karch, 2002; Schifano, 2004; Darke et al., 2007; Rosenson et al., 2007). The environment in which MDMA is taken is thought to play a role in deaths due to hyperthermia and hyponatraemia, with high ambient temperatures and physical exertion increasing the likelihood of these conditions occurring (Kalant, 2001; Gowing et al., 2002; Patel et al., 2005a,b; Darke et al., 2007; Rosenson et al., 2007). Hyperthermia, however, can also occur in quiet settings (Gowing et al., 2002; Patel et al., 2005a,b).

Like methamphetamine, MDMA increases heart rate, blood pressure and myocardial oxygen demand (Lester et al., 2000; Karch, 2002). As such, acute MDMA toxicity can result in serious, and potentially fatal, cardiovascular complications, such as cardiac arrhythmias, tachycardia in particular, and hypertension (Burgess et al., 2000; Kalant, 2001; Karch, 2002; Schifano, 2004; Liechti et al., 2005). Aortic dissection (Duflou and Mark, 2000) and acute myocardial infarction induced by MDMA have been reported (Qasim et al., 2001; Lai et al., 2003), but appear to be relatively rare events. Intracranial haemorrhage in association with MDMA use has also been reported (Milroy et al., 1996; Gowing et al., 2002; Karch, 2002; Schifano, 2004) and, whilst there is typically an underlying aneurysm or arteriovenous malformation, MDMA-induced hypertension increases the risk of such an event (Kalant, 2001; Karch, 2002).

Mortality rates associated with illicit drug use are consistently found to be highest among opioid users, with elevated rates of death also found among amphetamine and cocaine users (Darke et al., 2007). In 2005, among those aged 15–54 years, the rate of drug-induced deaths in Australia due to opioids was 32.5 per million persons. The rate of deaths due to methamphetamine and cocaine in 2005 was 5.9 and 1.3 per million persons, respectively (Degenhardt and Roxburgh, 2007a,b). To date, however, there are no national data on rates of MDMA-induced mortality among Australians and no cohort studies examining mortality rates among MDMA users. As such, the extent of MDMA-related mortality in Australia is unknown.

Whilst reports of MDMA-related death are far less common than those of opioid, amphetamine and cocaine-related deaths, the number of MDMA-related deaths appears to be increasing (Gill et al., 2002; Gowing et al., 2002; Karch, 2002; Schifano et al., 2003a,b, 2006; Patel et al., 2004; Schifano, 2004; Darke et al., 2007). Deaths related to MDMA appear to have been primarily due to the toxic reactions described above (Kalant, 2001; Gill et al., 2002; Liechti et al., 2005; Darke et al., 2007), although several deaths due to lethal injuries whilst the deceased person had been under the influence of MDMA (e.g. motor vehicle accidents, falls) have been reported (Kalant, 2001; Gill et al., 2002; Patel et al., 2004). Little is known, however, about the nature of MDMA-related mortality. To date, data on mortality associated with MDMA has been largely limited to single case reports and small-scale case series (Schifano, 2004; Darke et al., 2007). Although larger case series have been conducted in the UK (Schifano et al., 2003a,b) and US (Patel et al., 2004), they have only provided demographic and toxicological findings, and limited information regarding the circumstances of death. Whilst toxicological findings are an essential component of any investigation into cause of death, they are often difficult to interpret in isolation. Autopsy findings play a major role in determining the cause of death and help put toxicological findings into context. There is a paucity of data, however, on the prevalence of pre-existing and perimortem organ pathology among MDMA-related fatalities, with autopsy findings only published as part of single case reports or small-scale case series [e.g. Milroy et al., 1996; Lora-Tamayo et al., 1997; Duflou and Mark, 2000; Raikos et al., 2002; Libiseller et al., 2005].

The current study aimed to investigate the circumstances, toxicology, and associated organ pathology of MDMA-related deaths in Australia across a 5-year period. Specifically the study aimed:

1. To determine the number of MDMA-related fatalities that occurred in Australia between 1 July 2000 and 30 June 2005.
2. To describe the demographic characteristics of decedents and the circumstances of death.
3. To examine toxicological findings from MDMA-related fatalities.
4. To describe the major autopsy findings from MDMA-related fatalities.

2. Methods

2.1. National Coroners Information System

The National Coroners Information System (NCIS) is a centrally administered electronic database of coronial information provided by coroners' courts in each Australian jurisdiction. The NCIS contains information on deaths occurring from 1 July 2000 which have been reported to an Australian coroner. A complete NCIS case file includes demographic information, a police narrative of circumstances, autopsy and toxicology reports, and the coronial finding, which determines whether death was accidental, suicide or homicide, and confirms the medical cause of death. The medical cause of death is comprised of two parts:

I (a): Disease or condition directly leading to death.
I (b,c,d): Antecedent causes (morbid conditions, if any, giving rise to the direct cause of death).
II: Other significant conditions (contributing to death but not related to disease/condition causing death).

In Australia, the criteria for reporting a death vary between jurisdictions. In general, a death is reportable to a coroner where: the person died unexpectedly and the cause of death is unknown; the person died in a violent and unnatural manner; the person died during or as a result of an anaesthetic; the person was "held in care" or in custody immediately before they died; a medical practitioner has been unable to issue a death certificate stating the cause of death; the decedent's identity is unknown.

2.2. Case selection

MDMA-related deaths occurring between 1 July 2000 and 30 June 2005 were identified from the NCIS. Cause of death is determined by a forensic pathologist on the basis of the circumstances of death, an autopsy, and toxicological analyses. MDMA-related deaths were defined as those in which MDMA or MDA (methylenedioxyamphetamine), a primary metabolite of MDMA, was determined by the pathologist to have been a direct cause of death (i.e. directly leading to death), an antecedent cause of death (i.e. gave rise to the direct cause of death), or a significant contributing factor (i.e. contributed to death but not related to disease/condition causing death), as documented on the medical cause of death certificate. The direct and antecedent causes of death form what is known as the "morbid train of events" that led to death. Depending on the number of events culminating in death, the underlying cause of death will be either the direct cause of death (where no antecedent causes are noted) or the initial antecedent event. Where MDMA contributed to a motor vehicle accident causing death, only those cases in which the decedent was the driver of the car or a pedestrian were selected. That is, cases in which the decedent was the passenger in a car involved in a motor vehicle accident due to MDMA intoxication of the driver were not included.

2.3. Demographics and circumstances of death

Demographic information was extracted from each case file. The circumstances surrounding death were obtained from accompanying police reports, including, where available, the location of the fatal incident, evidence of drug use and route of drug administration, evidence of suicidal intent, drug treatment status, and recent prison history.

Table 1
Demographic characteristics of decedents.

	Females ($n=14$)	Males ($n=68$)	All cases ($n=82$)
Median age (years) (range)	22 (20–40)	28.5* (17–58)	26 (17–58)
Employment (%)			
Employed	43	75*	70
Retired/pensioner	0	3	2
Student	29	4	9
Unemployed	14	9	10
Unknown	14	9	10
Married/de facto (%)	8	20	18
Body mass index (mean) (range)	22.2 (19.7–27.1)	25.6* (17.4–43.6)	25.1 (17.4–43.6)
Treatment status (%)[a]			
In treatment	10	3	4
Type of treatment			
Methadone	10	2	3
Counselling	0	1	1

* Significant gender differences ($p<0.05$).
[a] $n=69$.

2.4. Toxicological results

Quantitative toxicological analysis is routinely conducted in cases of unnatural death, providing information on the blood concentrations of alcohol and other drugs. Recent use of MDMA was determined by the presence of MDMA, as well as MDA, its primary metabolite. Where both MDMA and MDA were detected, it was assumed that MDA was present as a metabolite, rather than ingested as a separate drug. Drug intoxication or toxicity causing or contributing to death is determined by the pathologist on the basis of the toxicological findings. Decisions about the role of drugs in death, however, are not based on toxicology results alone, with the consideration of other available evidence, such as autopsy findings, essential.

2.5. Autopsy reports

In cases of deaths referred to the coroner, a standardised medico-legal forensic autopsy is conducted, entailing a comprehensive examination of all major organs, including microscopy of representative tissue samples. This is a retrospective study. As such, the autopsies reported were not collected prospectively for the study, but were standard forensic autopsies performed as part of the medico-legal responsibilities of the forensic medicine departments in each jurisdiction. Where autopsy reports were available, information relating to the macroscopic and microscopic findings of major organ examination was reviewed.

Information on height and weight, from which body mass index (BMI) was calculated, findings of major organ pathology, and other clinically significant pathology was extracted from autopsy reports. Findings of particular relevance were: findings on cardiovascular, cerebrovascular, pulmonary, hepatic and renal pathology. Coronary atherosclerosis was classified as mild, moderate or severe on the basis of direct comment by the forensic pathologist in the post-mortem report, or as indicated by arterial stenosis ranges of 10–50% (mild), 51–75% (moderate) and >75% (severe).

2.6. Statistical analyses

For continuous variables, *t*-tests were employed. Where distributions were highly skewed, medians were reported. For dichotomous categorical variables, odds ratios (OR) and 95% confidence intervals (95%CI) were reported. In order to determine the variables that were independently associated with major organ pathology, simultaneous logistic regressions, using age, gender and BMI as independent variables, were conducted. All findings were examined for gender differences, and these are reported only where significant. All analyses were conducted using SPSS for Windows, Version 14.0 (SPSS Inc., 2006).

3. Results

3.1. Demographic characteristics

Eighty-two MDMA-related deaths were identified. MDMA was noted as a direct cause of death in 74.4% of cases, as an antecedent cause in 7.3%, and as a significant contributing condition in 18.3%. The median age was 26 years (SD 8.17, range 17–58 years) (Table 1). The majority were male (83%) and almost three-quarters were employed. Males were significantly older (Mann–Whitney $U=245.5$, $p<0.01$) and more likely to be employed (OR 4.00, 95%CI 1.21–13.18). The average BMI was 25.1 (SD 4.51, range 17.4–43.6), with males having a significantly higher BMI than females ($t_{55}=2.10$, $p<0.05$). A minority were in a married/de facto relationship and less than a twentieth were in treatment for drug dependence at the time of death (Table 1).

3.2. Direct causes of MDMA-related death

The direct causes of MDMA-related death are presented in Table 2. Cases in which MDMA was determined by a forensic pathologist to be a direct or antecedent cause of death have been separated from those in which MDMA was determined to be a significant contributing condition. It should be noted that there were several cases in which there was more than one direct cause of death. As such, the cause of death categories are not mutually exclusive and do not total 100%.

3.2.1. Cases where MDMA was noted as a direct or antecedent cause of death (n = 67). The direct cause of death among cases in which MDMA was a direct or antecedent cause of death was overwhelmingly drug toxicity (91%). Toxicity was attributed to MDMA alone in 25% of these cases, with combined drug (i.e. MDMA in combina-

Table 2
Direct cause of death according to role of MDMA.

Direct cause of death (%)	All cases ($n=82$)	
	%	*n*
Cases with MDMA as direct or antecedent cause of death ($n=67$)		
Drug toxicity	91	61
MDMA-only	25	17
Combined drug toxicity	66	44
Cardiovascular	10	7
Injury	9	6
Cerebrovascular	7	5
Aspiration of gastric content	4	3
Pulmonary	3	2
Drowning	3	2
Hyperthermia	1	1
Cases with MDMA as a significant contributing condition ($n=15$)		
Injury	47	7
Cardiovascular	13	2
Hanging	13	2
Carbon monoxide poisoning	13	2
Strangulation (homicide)	7	1
Cerebrovascular	7	1
Drowning	7	1

tion with other drugs) toxicity the cause of death in 66% of cases. The most common drugs present with MDMA in cases of combined drug toxicity were opioids (54%), methamphetamine (42%), benzodiazepines (23%) and alcohol (21%).

In 10% of cases, cardiovascular complications or disease arising from, or complicated by, MDMA use was a direct cause of death. Cardiovascular events and pathology causing death included coronary artery atherosclerosis/disease (6 cases), cardiomegaly (2 cases), probable cardiac arrhythmia (1 case), and acute thrombosis (1 case). In 7% of cases, cerebrovascular complications were a direct cause of death. Death in these cases was caused by cerebral haemorrhage (2 cases), brain swelling (1 case), hypoxic brain damage in association with combined drug toxicity (1 case), and structural cerebrovascular abnormalities (1 case).

Injury was a direct cause of death in 9% of cases. In 3 of 6 cases of injury, the injury was sustained in a motor vehicle accident. Other causes of injury were falls (1 case), self-inflicted knife wounds (1 case) and accidental asphyxia (1 case). In cases of MDMA-related death due to injury or homicide, the probable role of MDMA toxicity or intoxication is in causing impaired judgement and consequential increased risk-taking.

Other causes of death included aspiration of gastric contents (3 cases), pulmonary complications (bronchopneumonia) secondary to drug toxicity (2 cases), drowning (2 cases), and a single case of hyperthermia.

3.2.2. Cases where MDMA was noted as a significant contributing condition (n = 15). In almost half of the deaths in which MDMA was a significant contributing condition ($n = 7$), death was caused by injury. In 4 cases, fatal injuries were sustained in a motor vehicle accident. In 2 cases, one of which was a suicide, death was due to a fall. In 1 case, death was due to gunshot wounds (homicide).

Coronary artery disease arising from, or complicated by, MDMA use was a direct cause of death in two cases and cerebral haemorrhage was the direct cause of death in a single case. Other causes of death included hanging (2 cases), carbon monoxide poisoning (2 cases), drowning (1 case), and 1 case of homicide (strangulation).

3.3. Circumstances of death

In 9% of cases, death was by suicide, although, in a further 3 cases, intent was unable to be determined by the coroner (Table 3). Deliberate MDMA overdose was the method of suicide in 2 cases, hanging in 2 cases, carbon monoxide poisoning in 2 cases, and self-inflicted injury (fall) in 1 case.

Table 3
Circumstances of death.

	All cases ($n = 82$)
Location of fatal incident (%)	
Home	62
Public area	15
Road	10
Hospital	2
Other	11
Suicide (%)	
Yes	9
Unable to be determined	4
Route of administration (%)[a]	
Oral	98
Intravenous	2
Intranasal	0
Smoked	0

[a] $n = 64$.

The majority of fatal incidents occurred in a private home (Table 3). Public areas included trade/service areas and sports/recreation areas. Of the 64 cases where the route of MDMA administration was evident, oral ingestion was by far the most common route (Table 3). In 13% of the cases where MDMA was administered orally, however, there was evidence of injection of other drugs, such as syringes found in the vicinity, puncture marks found at autopsy, or a reported history of injecting drug use.

3.4. Toxicology

Quantitative toxicological analysis is routinely conducted in all cases of unnatural or unexpected death (i.e. deaths reportable to the coroner), providing information on the blood concentrations of alcohol and other drugs. Toxicological analysis entails screening for, and quantifying concentrations of, a range of licit and illicit substances, including MDMA and MDA. The results of these analyses are used to help determine cause of death. It is important to note that a drug may be detected in the blood at autopsy, yet not be considered by the pathologist to play a role in the cause of death. The presence and concentrations of MDMA and MDA were examined for all cases for which toxicology results were available, irrespective of the cause of death. The blood concentrations of MDMA and MDA, as well the prevalence of other drugs detected in the decedents' blood, regardless of whether or not they contributed to death, are presented in Table 4.

Toxicology reports, whilst completed for each case, were only available to the authors (i.e. attached to the NCIS case files for viewing) for 68 cases. Of these 68 cases, 97% of the blood samples tested positive for MDMA, 38% for MDA, and 37% for both MDMA and MDA. The median concentrations of MDMA and MDA were 0.85 mg/L (range 0.03–93.0 mg/L) and 0.10 mg/L (range 0.01–1.0 mg/L), respectively (Table 4). There were no significant differences between cases of death due to drug toxicity and cases of death due to injury or disease in the median concentrations of either MDMA (0.85 vs. 0.65, $p = 0.40$) or MDA (0.1 vs. 0.08, $p = 0.25$).

Other drugs were detected in 87% of cases, the most common being methamphetamine or its primary metabolite amphetamine, morphine and alcohol (Table 4). Females were significantly more likely to test positive for methamphetamine/amphetamine (OR 8.83, 95%CI 1.01–76.96) and miscellaneous other drugs (OR 5.5, 95%CI 1.14–26.63).

Table 4
Toxicological findings based on blood samples.

Drug detected	$n = 68$
Median blood concentrations	
MDMA (mg/L) (range)	0.85 (0.03–93.0)
MDA (mg/L) (range)	0.10 (0.01–1.0)
Presence of other drugs (%)[a]	87
Methamphetamine/amphetamine	50
Morphine	32
Alcohol	30
Codeine	25
Benzodiazepines	20
Antidepressants	18
THC	13
Cocaine/benzoylecgonine	10
Methadone	3
GHB	3
Ketamine	2
Antipsychotics	0
Miscellaneous other drugs (e.g. antihistamines, paracetamol)	20

[a] $n = 69$ (excerpt of toxicology results available from autopsy report for 1 case).

3.5. Major organ pathology

Full autopsy reports were available to the authors for 55 cases. In a further 6 cases, findings of major organ pathology were noted in the certified cause of death. Of those cases for which autopsy reports were available, 22% had no significant major organ pathology of any type. Information regarding the presence or absence of cardiac and cerebrovascular pathology was available for 57 cases. Cardiovascular pathology was noted in 58% of these cases, most commonly aortic and coronary artery atherosclerosis (44%), followed by cardiomegaly (18%) and ventricular hypertrophy (7%) (Table 5). Atherosclerosis was typically located in the coronary arteries (35%), with involvement of the aorta in 24% of cases. Atherosclerosis was moderate or severe in 23% of cases. Cerebrovascular pathology was noted in 12% of cases, and included hypoxia (5%), non-traumatic (4%) and traumatic (2%) cerebral haemorrhage, cerebral oedema (4%) and cerebrovascular malformations (4%).

In order to determine whether or not the presence of cardiovascular pathology was associated with some of the risk factors typical among the general population, multivariate logistic regression analyses were conducted, with age, gender and BMI entered as independent variables. These were not significantly associated with the presence of overall cardiovascular pathology. Similar analyses were conducted to determine the independent predictors of specific types of cardiovascular pathology (e.g. atherosclerosis, cardiomegaly and myocardial hypertrophy). Older age was associated with the presence of any atherosclerosis, i.e. mild, moderate or severe (OR 1.11, 95%CI 1.01–1.22), whilst a higher BMI was associated with moderate–severe atherosclerosis (OR 1.24, 95%CI 1.02–1.50). The presence of cardiomegaly and myocardial hypertrophy, however, were not significantly predicted by any of the aforementioned variables.

Information regarding pathology of other major organs was available in 56 cases. Hepatic pathology was observed in 31% of cases, with steatosis (26%) and histologic features of hepatitis C (HCV) infection (11%) the most prevalent forms (Table 5). Pulmonary pathology was noted in 29% of cases, with bronchopneumonia the most common finding (9%), followed by emphysema (4%). Renal pathology was noted in 7% of cases and was predominantly in the form of fibrosis (5%). Other organ pathology was noted in 5% of cases, and included pathology of the spleen (2%) and stomach (2%).

Table 5
Major organ pathology.

Type of pathology (%)	$n = 57$
Cardiovascular pathology	58
Atherosclerosis	44
Severity of atherosclerosis	
Mild	18
Moderate	9
Severe	14
Unspecified	2
Sites of atherosclerosis	
Coronary arteries	35
Aorta	24
Cardiomegaly	18
Ventricular hypertrophy	7
Ischaemic heart disease	6
Cerebrovascular pathology	12
Pulmonary pathology[a]	29
Hepatic pathology[b]	31
Renal pathology[c]	7

[a] $n = 56$.
[b] $n = 55$.
[c] $n = 55$.

3.6. Comparisons between MDMA-only and combined drug deaths

Cases in which MDMA was a direct or antecedent cause of death ($n = 67$) were selected for further analysis. Comparisons were made between cases where MDMA alone was the cause of death and cases where MDMA in combination with other drugs caused death (Table 6).

The MDMA-only and combined drug groups did not differ in terms of demographic characteristics or median blood concentrations of MDMA and MDA (Table 6). In order to determine whether or not death due to combined toxicity was associated with the presence of overall cardiovascular pathology, multivariate logistic regression analyses were conducted, with age, gender, BMI and combined toxicity (yes/no) entered as independent variables. Combined drug toxicity was the only significant predictor of overall cardiovascular pathology (OR 5.78, 95%CI 1.47–22.72). Similar analyses were conducted to determine the independent predictors of atherosclerosis, cardiomegaly and myocardial hypertrophy. Older age was associated with the presence of any atherosclerosis, i.e. mild, moderate or severe (OR 1.13, 95%CI 1.02–1.24), whilst combined drug toxicity was associated with moderate–severe atherosclerosis (OR 9.72, 95%CI 1.18–79.87). The presence of cardiomegaly and myocardial hypertrophy were not significantly predicted by any of the independent variables.

4. Discussion

MDMA has contributed to a clinically significant number of deaths in Australia. MDMA was a direct cause of death in the majority of cases, although, consistent with previous studies of MDMA and other drug-related fatalities (Gill et al., 2002; Schifano et al., 2003a,b; Patel et al., 2004; Darke et al., 2007), combined drug toxicity was more common than toxicity due to MDMA alone. Nevertheless, MDMA alone was a direct cause of death in over 1 in 5 cases. These findings indicate that MDMA toxicity is itself a primary cause of death and not merely a contributor to risk behaviours that result in death. In a minority of cases, however, MDMA toxicity or intoxication was a causal factor in death due to lethal injury.

Decedents were typically males in their mid to late twenties, a demographic profile similar to MDMA-related fatalities studied elsewhere (Darke et al., 2007), and the majority were employed. In Australia, regular MDMA users are usually male, aged in their mid-twenties and either employed or enrolled in tertiary education (Degenhardt and Dunn, 2007). As such, the decedents in the current study do not appear to differ demographically from living MDMA users. Contrary to the belief that MDMA-related deaths typically occur in particular environments, such as dance parties, where physical exertion combined with inadequate or excessive levels of hydration can lead to fatal hyperthermia and hyponatraemia, the majority of these deaths occurred in a private home. Moreover, there was only one documented case of death due to hyperthermia. These findings suggest not only that MDMA is used among a more heterogeneous population and wider variety of environments than the traditional image of MDMA as a “dance party drug” would suggest, but that the potential risks associated with the consumption of MDMA, particularly in conjunction with other drugs, are not limited to particular settings or activities of the user. As such, consideration of the morbidity and mortality associated with the use of MDMA should extend to all users and to use in a range of contexts.

Suicidal intent was evident in a minority of cases. The role of MDMA in the development of suicidal ideation and intent in these

Table 6
Comparisons between MDMA-only and combined toxicity cases for deaths where MDMA was a direct or antecedent cause of death.

	MDMA-only ($n = 19$)	Combined toxicity ($n = 48$)	All cases ($n = 67$)
Demographics			
Mean age (years) (range)	28.6 (20–50)	27.4 (17–45)	27.7 (17–50)
% Male	74	85	82
Blood concentrations[a]			
MDMA (median mg/L) (range)	0.7 (0.30–64.0)	0.9 (0.03–93.0)	0.85 (0.03–93.0)
MDA (median mg/L) (range)	0.11 (0.05–0.70)	0.10 (0.01–1.0)	0.10 (0.01–1.0)
Major organ pathology[b]			
Cardiovascular pathology	22	69*	59
Atherosclerosis	11	49	41
Severity of atherosclerosis			
Mild	11	12	12
Moderate	0	15	12
Severe	0	18	14
Unspecified	0	3	2
Cardiomegaly	0	24	19
Ventricular hypertrophy	0	6	5
Ischaemic heart disease	0	6	5
Cerebrovascular pathology	27	6	11
Cerebral haemorrhage	18	0	5
Pulmonary pathology	33	29	30
Hepatic pathology	0	42	33
Steatosis	0	33	26
Renal pathology	11	3	5

[a] $n = 54$.
[b] $n = 44$.
* $p < 0.05$.

cases is unclear, although cases of suicidal ideation and suicide following the use of MDMA have been documented (Cohen, 1996). As with all psychostimulants that are typically associated with a "euphoric" effect, MDMA can induce adverse psychological effects and users should be aware of this possibility.

The toxicological findings of cases were similar to those of other studies in that drugs other than MDMA, typically amphetamines, morphine and alcohol, were detected at autopsy (Gill et al., 2002; Schifano et al., 2003a,b; Patel et al., 2004; Darke et al., 2007). In contrast to MDMA fatalities in other countries (Gill et al., 2002; Schifano et al., 2003a,b; Patel et al., 2004), where cocaine toxicity is a common feature (Patel et al., 2004; Darke et al., 2007), cocaine was detected in a small minority of cases, reflecting the relatively low prevalence of cocaine use in Australia. The large proportion of deaths directly caused by combined drug toxicity reflects the fact that polydrug use is the norm among MDMA users (Schifano, 2004; Liechti et al., 2005; Degenhardt and Dunn, 2007). In cases where methamphetamine and ketamine toxicity contributed to death, however, it is difficult to determine whether or not the use of these drugs was intentional. Tablets sold as ecstasy often contain substances other than MDMA, such as methamphetamine, ketamine, MDA, PMA and MDEA (Quinn et al., 2004; Hall and Henry, 2006; Degenhardt and Dunn, 2007). Nevertheless, the fact that half of the toxicology reports noted the detection of methamphetamine in the blood is consistent with the polydrug use patterns of living MDMA users. In a recent survey of regular ecstasy users across Australia, over half (59%) reported methamphetamine use in the previous 6 months (Stafford et al., 2008).

The fact that opioids, ethanol and cocaine toxicity are frequently found among MDMA-related fatalities strongly suggests that using a combination of these drugs may increase the risk of lethal toxicity. Combined drug toxicity involving opioids and/or alcohol has been consistently demonstrated in studies of methamphetamine-related (Bailey and Shaw, 1989; Logan et al., 1998; Karch et al., 1999) and cocaine-related fatalities (Wetli and Wright, 1979; Bailey and Shaw, 1989; Tardiff et al., 1996; Coffin et al., 2003; Darke et al., 2005). Previous research has demonstrated that when methamphetamine is combined with opioids, cocaine or alcohol, toxicity is increased (Mendelson et al., 1995; Albertson et al., 1999; Darke et al., 2007; Kaye et al., 2007). Similarly, when cocaine is combined with opioids or alcohol, the resultant toxicity is greater than that due to each drug by itself (Kaye and Darke, 2004; Darke et al., 2007). It is reasonable to expect that when MDMA, which has similar stimulant properties to methamphetamine, is combined with such drugs, toxicity will likewise increase. It has been proposed that when MDMA is used with other stimulants, such as cocaine and methamphetamine, a synergistic interaction leads to an increase in the physiological effects of each drug (Gouzoulis-Mayfrank and Daumann, 2006; Schifano et al., 2006). Indeed, alcohol is known to potentiate the physiopathological effects of MDMA (Schifano, 2004; Darke et al., 2007).

In accordance with previous research (Milroy et al., 1996; Gill et al., 2002; Gowing et al., 2002; Gable, 2004; Hall and Henry, 2006), cases displayed a wide range of MDMA concentrations. Moreover, MDMA/MDA concentrations did not significantly differ between toxicity-induced deaths and deaths due to injury or disease, nor between MDMA-only deaths and combined toxicity deaths. There does not appear to be a clear dose–response for MDMA toxicity (Kalant, 2001; Gowing et al., 2002; Karch, 2002; Darke et al., 2007), with frequent overlap between lethal and non-lethal blood concentrations of MDMA (Kalant, 2001; Gowing et al., 2002; Karch, 2002). As such, MDMA concentrations should not be interpreted in isolation from other factors.

Pre-existing pathology is another factor that complicates the dose–response relationship. There is strong evidence to suggest that the chronic use of methamphetamine and/or cocaine can cause the premature and accelerated development of coronary artery disease and cardiomyopathy, and that pre-existing cardiac pathology can be exacerbated by use of these drugs (Logan et al., 1998; Karch et al., 1999; Karch, 2002; Kaye et al., 2007). Coronary artery disease,

for example, has been found to occur at a far greater rate among methamphetamine users than among age-matched controls, and at a significantly younger age than among the general population (Karch et al., 1999; Karch, 2002). In a study of methamphetamine-related deaths, Karch et al. (1999) found moderate–severe coronary artery disease in 16% of cases with a mean age of 36.8 years.

MDMA may also have cardiotoxic effects and may similarly exacerbate pre-existing cardiac pathology (Milroy et al., 1996; Qasim et al., 2001; Gowing et al., 2002; Patel et al., 2005a,b). Cardiovascular pathology was detected in almost 6 in 10 of the autopsies reviewed for the present study. Almost a quarter of decedents had moderate or severe atherosclerosis, and nearly 1 in 5 cases had cardiomegaly. These findings are consistent with those of autopsy studies of cocaine and methamphetamine users (Logan et al., 1998; Karch et al., 1999; Zhu et al., 2000; Karch, 2002; Darke et al., 2005; Kaye et al., 2007, 2008) and, more recently, MDMA users, in whom higher rates of cardiomegaly and myocardial hypertrophy have been found at autopsy (59% of MDMA-positive vs. 19% of MDMA-negative fatalities) (Patel et al., 2005a,b).

Given that decedents in the present study were relatively young – mostly in their twenties and early thirties – this type of pathology would appear to be more prevalent than would be expected among a general population sample of a similar age. Cardiomegaly, however, is an abnormal finding, irrespective of age (Karch et al., 1999). Moreover, the levels of cardiovascular pathology found among MDMA, cocaine and methamphetamine-related fatalities are substantially greater than those among opioid (29%) and non-drug-related fatalities (24%) (Darke et al., 2005; Kaye et al., 2008). These differences suggest that psychostimulant use in particular, rather than illicit drug use *per se*, may be associated with an increased risk of the development or exacerbation of such pathology.

Cardiovascular pathology was more prevalent among deaths due to combined drug toxicity than among those due to MDMA alone. Combined toxicity was an independent predictor of overall cardiovascular pathology and of the presence of moderate–severe atherosclerosis in particular. As such, the role of other drugs (e.g. methamphetamine, cocaine and nicotine) in contributing to such pathology cannot be discounted. Nevertheless, using MDMA in the presence of pre-existing pathology, alone or with other drugs, may increase the likelihood of an acute event.

Whether the cardiovascular pathology observed in this sample was due to chronic past use of MDMA, the use of other psychostimulants, or to other risk factors, such as smoking, the potential cardiotoxicity of MDMA has been well-documented in the literature. The risk of cardiovascular complications occurring is unable to be determined purely on the basis of dose and level of use. Other factors, such as individual variations in responsiveness, tolerance, and pre-existing cardiovascular health, interact to play an important but unquantifiable role in the physical reaction to any one occasion of use. For this reason, information about the potential for MDMA to induce or exacerbate cardiovascular pathology should be targeted to all users of the drug, not just chronic users.

Cerebrovascular pathology was evident in a minority of cases. Whilst non-traumatic cerebral haemorrhage and cerebral oedema induced by MDMA has been reported elsewhere (Milroy et al., 1996; Gowing et al., 2002; Karch, 2002; Schifano, 2004), there was a relatively low prevalence of such pathology among this case series. A higher rate of cerebrovascular pathology has been found among methamphetamine-related fatalities (Kaye et al., 2008), suggesting that the risk of cerebrovascular accidents is greater with methamphetamine than with MDMA. Indeed, the association between methamphetamine use and cerebrovascular accidents has been widely documented (Kalant and Kalant, 1975; Logan et al., 1998; Petitti et al., 1998; Karch et al., 1999; Zhu et al., 2000; Westover et al., 2007).

Levels of other major organ pathology, particularly hepatic pathology, were lower among MDMA fatalities than those observed among methamphetamine-related fatalities in Australia (Kaye et al., 2008). Nevertheless, a third of decedents had some form of hepatic and/or pulmonary pathology. The types of hepatic pathology detected were typically chronic changes, rather than the acute toxicity that has previously been associated with MDMA (Milroy et al., 1996; Kalant, 2001; Gowing et al., 2002; Darke et al., 2007). Without collateral information as to the presence of other risk factors for pre-existing pathology and the extent of other drug use, it is difficult to determine why rates of hepatic, pulmonary and renal pathology would be higher among methamphetamine-related fatalities, although decedents in the present study were, on average, younger than those in the methamphetamine fatality study (26 median years vs. 31 median years) (Kaye et al., 2008).

The main limitation of the current study is that NCIS case files were often incomplete. Information pertaining to risk factors for cardiovascular and cerebrovascular pathology, such as smoking and a positive relevant family history, was also unavailable, as was the extent of past drug use. Such information, however, is unlikely to be obtained from any retrospective study based on coronial files. Prospective cohort studies may provide a better understanding of the interaction between MDMA use and other mortality risk factors.

In order to determine the effect of long-term MDMA use on the development of chronic cardiovascular pathology (e.g. coronary artery disease), longitudinal cohort studies of MDMA users are recommended. Such studies may be able to control for the effects of other risk factors, such as family history, smoking and other drug use in particular.

The current study is the most comprehensive large-scale examination of MDMA-related mortality to date. This study indicates that in Australia, as elsewhere, MDMA contributes to a clinically significant number of fatalities. Overall, the current study highlights the need to educate users about the potential harms of MDMA use, particularly that in conjunction with other stimulants, opioids and alcohol, which are known to increase the net toxicity.

Role of funding source

Funding for this study was provided by the Australian Government Department of Health and Ageing (AGDHA). The AGDHA had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Contributors

Shane Darke, Johan Duflou and Sharlene Kaye designed the study and wrote the protocol. Sharlene Kaye managed the literature searches and summaries of previous related work, undertook the statistical analysis, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

Acknowledgements

This research was funded by the Australian Government Department of Health and Ageing. The authors would like to thank the NCIS staff at the Victorian Institute of Forensic Medicine, particularly Marde Hoy, Jessica Pearse and Stephen Morton, for their assistance with data searches and retrieval.

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ATTACHMENT 5

Bruker Alpha II not adequate for 3 or more adulterants

From: Andrew Leibie [mailto:andrew.leibie@swlabs.com.au]
Sent: Thursday, March 14, 2019 4:30 PM
To: Gary Christian
Subject: RE: Questions regarding Pill Testing and their Bruker Alpha II

Forgive me, I'm not certain of your background so I'm not sure how detailed to make this explanation, but I can comment on the para below you have provided. I've also attached a briefing paper I put together on this topic, it's intended to be as "non scientific" as I can make it, but it's intended to really try and highlight the shortcomings in the current approach of testing only on site without access to a sophisticated laboratory. In addition, I have a presentation I provided to a pill testing forum in Melbourne recently hosted by the Pennington Institute As to your points below:

This could arise due to the sample being an impure mixture of more than one compound

This is a known issue for FTIR. Once you get more than 3/4/5 compounds present, the spectra (ie the IR light reflected off the sample) becomes too complex for the algorithms to identify. It's not so much about the amount of individual drugs present, as to how "noisy" the output is. This is a real problem for illicit pill testing as you can imagine there is typically a lot of contamination from other fillers, poor hygiene, solvent residues etc that would not be present in a commercial drug manufacturing process.

due to the major compound not being included in the spectra libraries

This is another problem, essentially the FTIR process is only as good as the library of drugs it contains. While this isn't an issue for our common drugs (MDMA, Methamphetamine etc) for the new psychoactive substances (which are particularly dangerous) it's highly unlikely to have them in it's library to match the spectra against. A lot of 'noise' that it can't identify may well be other drugs present in the sample but not in the instrument library.

Does that make sense? Where did you source this information from by the way? I've not seen it before?

As to 53% not meeting their quality threshold – suffice to say that means that 53% of the samples tested you really have no way of being confident in your results. It may be that the result identifies MDMA, but not other drugs present. Or, it could be that the MDMA result is actually due to another drug being misidentified, such as PMA, which is a far more dangerous proposition (see https://en.wikipedia.org/wiki/Para-Methoxyamphetamine)

ATTACHMENT 6

Bruker Alpha II may not have fully current database of newer drugs

See John Lewis' article from the Australian on the next page

PILLS WILL KILL, BUT TESTING

On-site 'labs' checking the content of illegal drugs seem sensible, but the idea is daft

JOHN LEWIS The Australian
Jan 16 2019 PAGE 10

The notion of testing illegal pills to see if they are safe is gaining momentum in the wake of a spate of deaths of young people at music festivals around Australia.

Ross Fitzgerald argued in support of it on this page yesterday.

But it won't work and is fraught with dangers. What if we don't know what we are testing for? New psychoactive compounds are being developed all the time. In any case, is the drug we're testing for consistent throughout the pill? We could easily miss it by scraping a little from the surface. And perhaps the deadly threat lurks in unidentified contaminants.

There is much to be considered — maybe first is the fact no forensic toxicologist I know recommends pill testing or believes it is practical.

Years ago, most people were happy taking amphetamine, cocaine and occasionally LSD in addition to alcohol; in the past few years novel psychoactive substances have become a clinical and forensic nightmare. These drugs include synthetic cannabinoids, such as PB-22, cathinones (stimulants related to the khat plant that mimic the effects of methylamphetamine and cocaine) and a number of synthetic benzodiazepines drugs (related to diazepam).

Consider this: in 2010 there were about a dozen synthetic "spice type" cannabinoids; by 2011 there were about 40; in 2012 there were 60. In 2015 four Australians died from PB-22. By 2016 there were about 125 synthetic cannabinoids, more than 20 cathinones, 20 synthetic benzodiazepines, and by last year about 18 highly potent fentanyl derivatives were found in the US. There have been reported deaths because of the synthetic cathinone MDPV in Italy and carfentanil-laced heroin in Britain. Carfentanil is a fentanyl-like substance 10,000 times as potent as morphine and has been deemed responsible for inadvertent overdoses by regular heroin users. It is estimated that a lethal dose of this drug may be as low as 20 micrograms. Local authorities have already seized shipments of carfentanil. These highly potent substances are mixed with regular benzodiazepines or ecstasy.

Fitzgerald states the risks of pill testing appear to be minimal. That is curious. In a recent toxicology publication, a leading forensic scientist reported there was great concern in the US that these novel illicit substances typically are outside the scope of routine drug testing by hospitals and laboratories or below the sensitivity levels for detection. If major forensic facilities have difficulty in identifying these substances, it stands to reason that on-site pill testing could not adequately identify most of the potentially lethal components in a pill scraping.

In another recent publication, Australian forensic laboratories noted there were about 740 new psychoactive substances reported to the UN Office on Drugs and Crime from 2009 to 2016.

Again, leading Australian forensic institutions using high-resolution mass spectrometry struggle to keep up with ever-increasing variations in synthetic substances.

THEM IS NOT YET THE ANSWER

The issue of pill testing should be decided on forensic science

Pill testing may identify some of these within the time and scope of the on-site facility, but the risk of an adverse or fatal episode remains with several hundred substances not detected.

Fitzgerald reckons there is a strong case from more than two decades of experience in Europe, but that's ignoring the exponential increase in deadly adulterants.

The issue of pill testing should be decided on forensic science. The ability to identify a wide range of components in a compound depends on the ability to test a representative portion of the substances, and that representation is incumbent on the pill being homogeneously mixed when produced. If the pill has not been manufactured to ethical pharmaceutical standards then there is a risk of the pill tester missing the more toxic ingredients of the substances.

If pill testing were trialled, you would need sophisticated instrumentation such as high-resolution mass spectrometry to rapidly analyse the contents of the unknown substance. Such instrumentation is not amenable to on-site music festival venues. Critically, operators of the instrumentation would need to ensure their database of compounds is up to date. As newer synthetic drugs are regularly entering the market, forensic laboratories are struggling to obtain appropriate and expensive analytical reference material to identify unequivocally all ingredients in a pill.

To date, analytically trained experts have yet to explain adequately the complexity of attempting to test pills reliably and quickly at an on-site venue to be reasonably confident they can eliminate minute amounts of potentially lethal ingredients such as the deadly carfentanil.

In any case, the greater difficulty is in figuring out where in the pill, whether purportedly ecstasy or methylamphetamine, might lie the adulterants. Only forensic analysis can determine the concentration of adulterants in pills. For many of these substances, there is no known toxic concentration. When combined with other substances, adverse effects including respiratory depression leading to coma can occur at any level.

Before moving ahead with a policy to trial pill testing, we need some sobering facts. The efficacy of pill testing is best left to forensic scientists, while the value of pill testing as a means of harm reduction is the domain of researchers into behavioural patterns of users and their potential for risk-taking. A 2004 study by the National Drug and Alcohol Research Centre into risk factors and risk perceptions found that those who perceived the possibility of getting caught or being involved in accidents were less likely to drive while impaired. Conversely, the perception of not getting caught or having an adverse reaction contributed to their drug-taking behaviour.

While one cannot draw a direct correlation between drugs and driving and taking of unknown pills at a music festival, it is clear from recent events that many attendees at these events do not perceive the dangers and non-forensic pill testing may well provide attendees with a false sense of security.

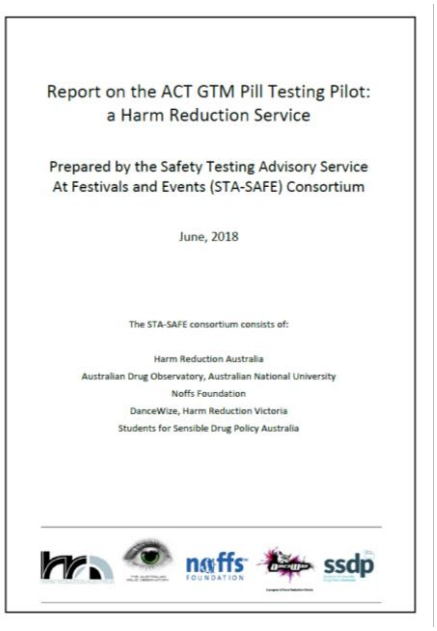
John Lewis is honorary associate at the Centre for Forensic Science at the University of Technology Sydney

ATTACHMENT 7

Bruker Alpha II failed to determine 53% of substances in Canberra trial

From page 20 of the Canberra STA-SAFE pill testing trial evaluation document found at https://www.harmreductionaustralia.org.au/wp-content/uploads/2018/06/Pill-Testing-Pilot-ACT-June-2018-Final-Report.pdf

Screenshot of the STA-SAFE document with our markup below:



Report on the ACT GTM Pill Testing Pilot:
a Harm Reduction Service

Prepared by the Safety Testing Advisory Service
At Festivals and Events (STA-SAFE) Consortium

June, 2018

The STA-SAFE consortium consists of:

Harm Reduction Australia
Australian Drug Observatory, Australian National University
Noffs Foundation
DanceWize, Harm Reduction Victoria
Students for Sensible Drug Policy Australia

There were five instances where the second ranked compound had a hit quality score above the cut-off (>750). In each case this second match identified the same compound indicating that the libraries contained several different spectra for the same substance. There were four instances where the second and third ranked compounds had hit quality scores above the cut-off (>750). Again, these matches identified the same compound. There was no case of multiple hit quality scores above cut-off (>750) that identified different compounds.

For 53% of samples tested, none of the hit quality scores were above the threshold. This increased the uncertainty surrounding compound identification. This could arise due to the sample being an impure mixture of more than one compound, or due to the major compound not being included in the spectra libraries. Although hardware limitations prevented the use of mixture analysis or spectrum subtraction and re-matching on the day of the pilot, such an approach could be used in future to more closely evaluate sample composition where hit quality scores are low. An example of this approach is given above for GTM001. In this case the highest hit quality score was only 359 and identified MDMA as the major component (figures 5, and 6). Later mixture analysis conducted after the pilot identified dimethyl sulfone, a common cutting or filling agent, as the second component (figures 7 and 8).

ATTACHMENT 8

Pill testing removes perceived impediments to drug taking

Below are the statistics from the 2016 National Drug Strategy Household Survey regarding factors influencing a decision not to try an illicit drug.

Table 5.64: Factors influencing the decision never to try an illicit drug, people who have never used aged 14 years or older, 2007 to 2016 (per cent)

	Persons			
Factor	**2007**	**2010**	**2013**	**2016**
For reasons related to health or addiction	41.4	47.0	42.8	43.2
For reasons related to the law	22.5	28.6	29.1	31.1#
Didn't want anyone to find out	4.1	5.2	3.8	3.8
Didn't like to feel out of control	16.3	22.4	24.2	24.5
Pressure from family or friends	9.3	10.8	9.5	10.5
Didn't think it would be enjoyable	13.1	17.8	17.8	19.3#
Just not interested	63.1	73.3	76.1	73.4#
Financial reasons	5.1	6.7	5.2	6.4#
No opportunity or illicit drugs available	5.5	5.4	4.8	5.0
Religious/moral reasons	15.4	19.1	22.4	22.9
Fear of death	12.3	17.6	18.1	18.2
Other	6.7	2.9	2.1	2.7#
Don't know	0.2	4.2	3.9	5.3#

Statistically significant change between 2013 and 2016.

Notes:

1. Base is those who had never used an illicit drug in their lifetime.

2. Respondents could select more than one response.

Source: NDSHS 2016.

Yet pill testing advocates offer clearly false assurances. Dr Alex Wodak, one of Harm Reduction Australia's most visible and vocal advocates says that,

> "In the current debate, ministers argue that the "best" we should aim for is that young people attending music dance events would lose their desire to take drugs at these events and that law enforcement would make these drugs

> virtually unavailable. A more realistic appraisal is that young people will continue to want to take drugs, police will continue to be unable to substantially reduce the availability of drugs *and that pill testing will substantially reduce, but not eliminate, the risks of drug taking* (our emphasis)."
> https://www.smh.com.au/national/the-simple-question-mps-opposed-to-pill-testing-should-ask-themselves-20180916-p50427.html

Clearly, when MDMA is causing almost all Australian pill tests, Dr Wodak could not possible claim that pill testing 'will substantially reduce' the risks of drug-taking. Only abstinence, not taking MDMA will do that. Yet Dr David Caldicott, another high-profile advocate, ridicules abstinence, teaching that users can still be getting their MDMA high while using more safely.

> "However, Dr Caldicott says this is an extremely outdated approach that's as practical as trying to get young people to abstain from sex before marriage. "We're kind of like the condoms of the harm reduction world. *We're trying to keep people safe*," he explains."
> https://www.vice.com/en_au/article/nny3ax/pill-testing-is-to-be-introduced-at-music-festivals-around-australia

ATTACHMENT 9

Pill testing advocates promoting CANNABIS LEGALISATION

Dr David Caldicott – Harm Reduction Australia

Dr David Caldicott, the clinical lead at the ANU's Australian Medicinal Cannabis Observatory told *The RiotACT* a bill like Mr Pettersson's could limit the drug's availability to underage consumers and undermine the illicit drug market in the ACT.

"From a public health perspective, there are merits to an argument of a regulated market. It is likely to be met by howls of abuse from more conservative commentators who probably don't understand the policy implications," he said.

"The likelihood is that overall it will reduce the harm from drugs. Very few people would argue that increased availability of cannabis would make the city a healthier environment but it is entirely possible that regulating the environment will make cannabis less available."
https://www.news.com.au/lifestyle/health/bill-to-legalise-recreational-marijuana-in-act-has-overwhelming-support/news-story/19712dfb54be37c49864327a52ad4aec

Dr Alex Wodak – Australia21

"If regulated MDMA was produced, MDMA sold legally, we'd hardly hear of it from one year to the next in terms of casualties. There'd still be some casualties but they'd be pretty uncommon," he claimed.

Dr Wodak said the "proper regulation" of cannabis and MDMA would lower the risks of the drugs and pharmacies could be a place to sell the pills.
https://www.dailytelegraph.com.au/news/nsw/drug-reform-campaigner-dr-alex-wodak-wants-mdma-to-be-regulated-and-sold-in-stores/news-story/89fe87513583d2805ed4e069b20b6922

Gino Vumbaca – President, Harm Reduction Australia

Expert endorsement for Just Legalise It

The health, social and economic harms of our current approach to cannabis cannot be underestimated – every year more than 80,000 people are arrested for the possession or use of cannabis. Each conviction providing untold long-term harm to careers, travel and family. Given millions of Australians have used, and many continue to use cannabis, surely the goal of this harmful criminalisation approach cannot be to arrest and ruin the lives of millions of Australians?

The level of harm inflicted on so many people, for so many years, just for using cannabis simply has to stop.

Harm Reduction Australia welcomes the sensible and evidence-based approach of the Greens to cannabis.

Gino Vumbaca
President of Harm Reduction Australia

https://drugs.org.au/just-legalise-it/

Mick Palmer – Australia21

'A former Australian Federal Police commissioner has backed prominent harm minimisation advocate Alex Wodak's call to regulate MDMA.

Mick Palmer, who had a distinguished 33-year career as a police officer, said he was in favour of the cautious regulation of drugs such as ecstasy and cannabis.

"Unless we find ways to regulate the sale of illicit drugs and turn the current black market into a white market, we'll never get on top of this problem, there's no doubt about that," Mr Palmer said.'
https://www.canberratimes.com.au/national/former-top-cop-backs-dr-alex-wodak-s-call-to-regulate-mdma-20190130-p50ugj.html

ATTACHMENT 10

Journal study with typical range of MDMA blood concentrations

See page 679 of the following pdf of the British Journal of Anaesthesia, where it details the typical range of blood concentrations at death as 0.1 mg/litre – 2.4 mg/litre, where the median average for drug toxicity amongst the 82 Australian deaths studied (Attachment 4) was 0.85 mg/litre, well within the typical range of 0.1-2.4 mg/litre.

British Journal of Anaesthesia **96 (6)**: 678–85 (2006)
doi:10.1093/bja/ael078 Advance Access publication April 4, 2006

BJA

REVIEW ARTICLE

Acute toxic effects of 'Ecstasy' (MDMA) and related compounds: overview of pathophysiology and clinical management

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Since the late 1980s 'Ecstasy' (3,4-methylenedioxymethamphetamine, MDMA) has become established as a popular recreational drug in western Europe. The UK National Criminal Intelligence Service estimates that 0.5–2 million tablets are consumed weekly in Britain. It has been reported that 4.5% of young adults (15–34 yr) in the UK have used MDMA in the previous 12 months. Clinically important toxic effects have been reported, including fatalities. While the phenomenon of hyperpyrexia and multi-organ failure is now relatively well known, other serious effects have become apparent more recently. Patients with acute MDMA toxicity may present to doctors working in Anaesthesia, Intensive Care and Emergency Medicine. A broad knowledge of these pathologies and their treatment is necessary for anyone working in an acute medical speciality. An overview of MDMA pharmacology and acute toxicity will be given followed by a plan for clinical management.

Br J Anaesth 2006; **96**: 678–85

Keywords: complications, convulsions; complications, death; complications, hepatotoxicity; complications, hyperthermia; complications, hyponatraemia; toxicity, 3,4-methylenedioxymethamphetamine, MDMA (Ecstasy)

Ecstasy (3,4-methylenedioxymethamphetamine, MDMA) has been described as 'the love drug' and is also known under a number of other names including 'XTC', 'Adam' or simply 'E'. It became established as a dance drug, popular at 'rave' parties and is taken for its mood-enhancing properties, principally the 3 Es; energy, empathy and euphoria.[14] According to the British Crime Survey for 2000, 5% of 16–19-yr-olds use Ecstasy.[34] In England during 1995–6 there were 18 deaths related to Ecstasy.[19] From 1997 to 2000 there were 81 Ecstasy-related deaths in England and Wales.[59] The risk of death for first-time users has been estimated to be between 1 in 2000 to 1 in 50 000.[19]

The immediate effects of Ecstasy vary from almost universal minor symptoms to those that are rare but potentially life-threatening. Minor side-effects include trismus, tachycardia and bruxism. Delayed effects include midweek 'lows' and a prolonged 'hangover' that may last up to 5 days.[11 52] Severe effects include sudden death, hyperpyrexia, rhabdomyolysis and multi-organ failure, the serotonin syndrome, isolated liver failure, an acute panic disorder and hyponatraemia with cerebral oedema (Table 1). An additional association and possible causation in morbidity and mortality related to trauma is hard to quantify. It has been reported that recreational drugs have become a major associated factor in fatal road traffic accidents.[61]

Pharmacology and pharmacokinetics

Over 16 'Ecstasy'-related compounds have been identified. These include its 'sister' drug 3,4-methylenedioxyethamphetamine, MDEA, 'Eve' and their common metabolite 3,4-methylenedioxyamphetamine, MDA, 'Ice' (Fig. 1). Tablets sold as Ecstasy may contain varying amounts of MDMA (typically 30–150 mg) or none at all. Other MDMA-related compounds may be sold as Ecstasy, and 'Ecstasy' tablets have also been found to contain a variety of other drugs including amphetamine, methamphetamine, caffeine, ketamine and acetaminophen.[76]

MDMA causes the release of serotonin (5-hydroxytryptamine; 5-HT), dopamine and norepinephrine in the

Table 1 Major acute syndromes related to MDMA

Sudden death
Exertional hyperpyrexia leading to rhabdomyolysis and multi-organ failure
Serotonin syndrome
Hyponatraemia and cerebral oedema
Isolated acute liver failure
Cerebrovascular accidents
Acute anxiety and panic disorder

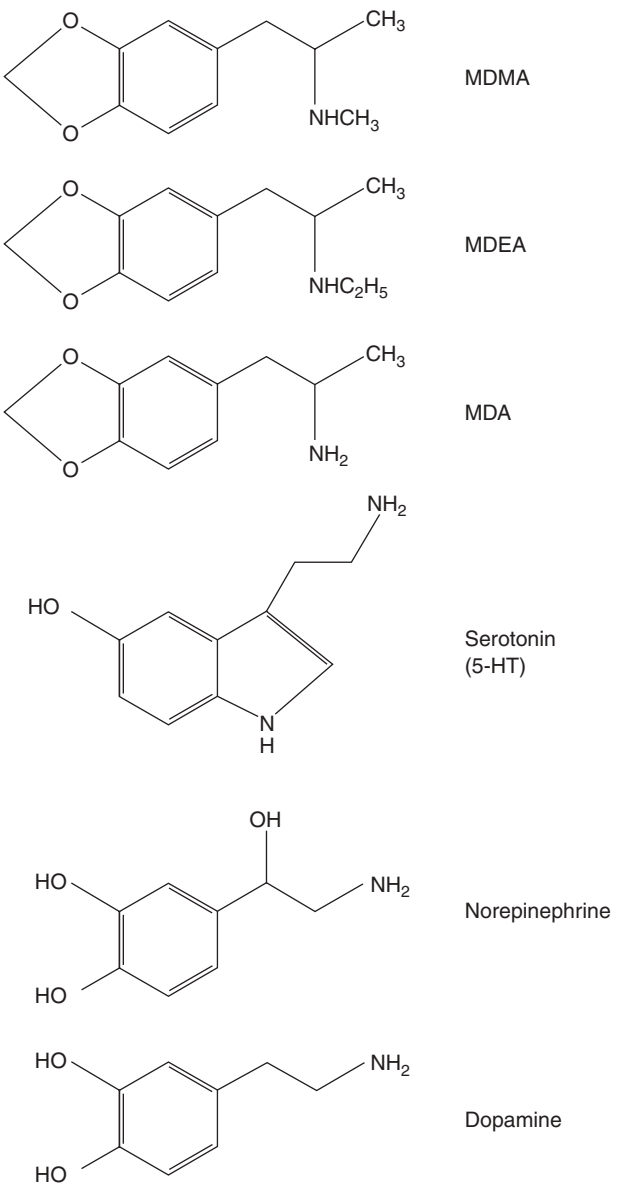

Fig 1 Chemical structures of MDMA (Ecstasy), MDEA, MDA, serotonin (5-HT), norepinephrine, and dopamine.

central nervous system. MDMA has also been shown to bind and inhibit their reuptake transporters at the synapse, principally with 5-HT.[20 44 68] There is thus an acute increase in the intra-synaptic concentration of these transmitters, followed by a period of depletion. The chemical structures of these important neurotransmitters are also shown in Figure 1. These compounds are involved in the control of mood but are also central to the mechanisms of thermoregulation and control of sleep, appetite, reward and the autonomic nervous system.[20 44] Additionally, after MDMA administration, there is an increase in blood levels of cortisol, prolactin, adrenocorticotropic hormone (ACTH), dehydro-epiandrosterone and antidiuretic hormone (ADH).[29 68] It has been suggested that the increase in prolactin may be responsible for the feeling of emotional closeness and may mimic the post-orgasmic state;[41 50] MDMA has slight monoamine oxidase (MAO) inhibiting activity and some direct activity at several receptor types (5-HT_2, M_1-muscarinic, H_1-histamine and α_2-adrenergic), the significance of which is not known.[68] MDMA has a plasma half-life of 7.6 h. Typically, after oral ingestion (75–150 mg), desired effects begin within 1 h and last 4–6 h.[68] Blood levels in asymptomatic users and those with serious side-effects are often similar, suggesting that adverse reactions are likely to relate to the circumstances in which the drug is taken, and that there may also be an idiosyncratic component.[28] A number of fatalities have been reported with blood levels of 0.1–2.1 mg $litre^{-1}$.[31] However, a case of a deliberate overdose of MDMA in which the blood level reached 4.3 mg $litre^{-1}$ with no more than mild sinus tachycardia and a degree of somnolence has been reported.[54] Another analytically documented overdose resulted in a plasma MDMA of 7.72 mg $litre^{-1}$, the highest recorded in a surviving patient, with just a 'hangover', tachycardia and hypertension.[31] The highest level reported in association with multi-organ failure in a subsequent survivor was 7 mg $litre^{-1}$.[6]

MDMA metabolism involves two main pathways. In one, *O*-demethylenation is followed by catechol-*O*-methyltransferase (COMT)-catalysed methylation and/or glucuronide or sulphate conjugation. In the other, *N*-dealkylation, deamination and oxidation is followed by conjugation with glycine. The cytochrome P450 isoenzyme CYP2D6 partially regulates the *O*-demethylenation pathway. As CYP2D6 displays genetic polymorphism in human subjects, it might be suspected that slow metabolizers are at a higher risk of acute MDMA toxicity. However, the formation of an enzyme–metabolite complex results in auto-inhibition that renders all subjects, regardless of genotype, phenotypically poor metabolizers after two consecutive doses. This limits the effect of CYP2D6 pharmacogenetic variation on the acute toxicity of MDMA.[58 68] COMT activity is also subject to genetic variation. This enzyme converts 3,4-dihydroxymethamphetame (HHMA) to 4-hydroxy-3-methoxymethamphetamine (HMMA). *In vitro* studies have shown that HMMA is even more potent than MDMA in releasing ADH. COMT polymorphism may thus contribute to inter-individual differences in ADH release after MDMA (see below).

There is considerable scope for interaction between Ecstasy and other drugs that affect these pathways.

Table 2 Minor clinical symptoms and signs seen with MDMA

Tachycardia	Elevated mood
Hypertension	Confusion
Mydriasis	Ataxia
Dry mouth	Nystagmus
Sweating	Bruxism (jaw clenching)

HIV-1 protease inhihitors (antiretrovirals) such as ritonavir are potent inhibitors of CYP2D6 and prolonged effects of a small dose of MDMA have been reported.[2 30]

Adverse effects

A number of minor clinical symptoms and signs in Ecstasy users relate to a disturbance in the central and autonomic nervous systems. The principal features are shown in Table 2.

An increased risk of trauma, particularly from road traffic accidents, is self-evident. This is particularly likely as most recreational drug users travel to venues, often by car because of late finishing times. They may combine Ecstasy use with that of other agents that may impair judgement, principally alcohol, marijuana and cocaine.[9]

An association between Ecstasy use and cerebral haemorrhage, cerebral venous sinus thrombosis, and aplastic anaemia has been reported.[18 26 33 37 56] There have also been a number of reports of pneumothorax and pneumomediastinum in Ecstasy users.[3 39 53] In one report, two cases occurred on the same evening among a group of friends.[55] It is thought that the mechanism of injury here relates to sustained physical activity with a closed glottis, a form of Valsalva manoeuvre. This can lead to alveolar rupture and subsequent tracking of air along the perivascular space. However, in one case, a small oesophageal tear was found.[55] All subjects reported recovered with conservative management, but most involved several days in hospital. They were investigated with chest radiographs and contrast swallow and treated with i.v. antibiotics when oesophageal injury was proven or suspected.

MDMA and sudden death

Little is known about the aetiology of sudden death in individuals who had taken MDMA. It seems likely that the sympathomimetic effects of the drug may precipitate a dysrhythmic catastrophe. This may occur in an otherwise perfectly healthy individual. However, undiagnosed cardiomyopathy, hypertension or viral myocarditis may be involved. A number of other congenital cardiac conduction abnormalities may go undiagnosed in young people (such as Wolff–Parkinson–White, Romano–Ward, Brugada, and Jervell and Lange–Nielsen Syndromes). These individuals are evidently at risk of sudden death from excessive sympathetic stimulation.[8 60 74] Furthermore, a long QT interval has been reported in association with MDMA toxicity.[27]

Hyperpyrexia, rhabdomyolysis and multi-organ failure

The syndrome of hyperpyrexia together with rhabdomyolysis and multi-organ failure is well described.[31] Most cases appear to be associated with excessive exertion with inadequate fluid replacement to facilitate thermoregulation. Some of these effects may be explained by the euphoric effects of the drug, accentuated by repetitive music and a crowded environment. It is known that both 5-HT and dopamine are involved in central control of thermoregulation and that MDMA effects lead to the activation of mechanisms that both conserve and generate heat. The serotonin syndrome is probably the most extreme of these effects. The occurrence of gross hyperpyrexia and its consequences in predominantly nightclub-going UK users, led to the suggestion that the circumstances in which the drug is taken is pivotal to the occurrence of this complication.[28] Users who spend the night dancing energetically in a warm environment predispose themselves to the development of exertional hyperpyrexia. There is an excess of deaths in relation to parties in the summer and at New Year.[59] Interestingly, laboratory studies with rats have shown that MDMA-induced hyperthermia in males is increased significantly in a warm environment, with overcrowding ('aggregation toxicity')[22] and by social interaction with a female.[7] A switching effect has been demonstrated whereby rats fail to show a hyperthermic response to MDMA if housed below 20°C.[22]

Patients present with hyperpyrexia, muscle rigidity, hyper-reflexia and are often subsequently found to have rhabdomyolysis. Impaired consciousness, disseminated intravascular coagulation (DIC) and multi-organ failure rapidly follow. Five organ-system failure is not unusual; some of these cases have survived after prompt treatment in an intensive care environment.[24] The height and duration of hyperpyrexia are indicators of the risk of mortality. There are few survivors if the peak core temperature exceeds 42°C, though the highest recorded value in a survivor reached 42.9°C.[36] Rhabdomyolysis can be pronounced, with peak creatine phosphokinase (CPK) levels in the region of 30 000–100 000 u litre^{-1}. The highest recorded peak CPK in a survivor is 555 000 u litre^{-1}.[25]

Denborough and Hopkinson[12] suggested that there might be a direct effect of Ecstasy on muscle. They showed some augmentation of the halothane and caffeine induced muscle contraction produced *in vitro* while testing muscle biopsy specimens in the investigation of possible malignant hyperthermia (MH). However, this work has been criticized for using concentrations of MDMA up to 2000 times greater than that found in the plasma of Ecstasy-related fatalities.[23] More recent work, in a rat model, suggests that MDMA uncouples skeletal muscle mitochondria *in vivo*, but that this is the result of an indirect mechanism.[57]

The overlap in clinical features between MDMA-induced hyperthermia and severe heat stroke, neuroleptic malignant

syndrome, serotonergic syndrome and MH cannot be ignored. It may be that these pathological entities ultimately share a final common pathway associated with the consequences of extreme hyperthermia. All would agree, that rapid cooling measures are essential along with the support of failing organ systems. Dantrolene has been used in the treatment of Ecstasy-related hyperpyrexia. While of established benefit in MH, its use in these other conditions remains controversial. It has been suggested that dantrolene treats the effects and not the cause of hyperpyrexia and that it may be better to direct treatment at central mechanisms of thermoregulation.[48] It is, of course, difficult to perform a proper controlled trial when cases present *in extremis* and require urgent management. This is particularly so when they occur sporadically, across a variety of centres. However, this is not always the case with heatstroke. The use of dantrolene in the treatment of heatstroke has been investigated by the Heatstroke Centre in Makkah, Saudi Arabia. An experienced unit, they were able to study 52 patients over a 4 day period in a randomized double blind controlled trial.[5] Dantrolene made no difference to the rate of cooling. This group is, however, well-practised and has equipment for patient cooling not usually available in other countries, where severe heatstrokes occur less commonly.

A review of case reports over the initial 10 yr of widespread use of MDMA lends some support to the use of dantrolene. While an entirely arbitrary period, it allows for a reasonable number of cases to be considered. Cases described beyond this time have been excluded because dantrolene had become well established on the basis of anecdotal evidence and withholding the drug might suggest inadequate care on a number of levels. Cases reported over this period have been broken down into those with peak temperatures in the ranges 41–41.9°C and 40–40.9°C. Patients with a peak temperature of 42°C or more are considerably less likely to survive irrespective of treatment, while those with a peak of less than 40°C might not be expected to develop rhabdomyolysis and multi-organ failure. Peak temperatures in the range 41–41.9°C have been associated with 4/4 survivors in the dantrolene treated group and 2/5 in the non-dantrolene treated group.[6 25 31 45 62 72 77] In the lower range 40–40.9°C, there were 6/6 survivors with dantrolene and 4/5 without it.[4 15 31 46 62 64 66 72 73] Overall, considering cases in the range 40–41.9°C, there were 10/10 survivors with dantrolene treatment and 6/10 without. It has been noted that more rapid control of temperature was achieved in cases where dantrolene was used.[35 64] In most centres, where a patient is *in extremis*, requiring intubation, ventilation, transfer to intensive care facilities and the establishment of invasive monitoring and support, any aid to cooling at this critical time may be of benefit. Once hyperthermia occurs, the calcium requirement for excitation–contraction coupling is reduced, so that hyperthermia alone can cause a degree of muscle contraction with a consequent increase in heat production and metabolic demand. This added complication can be counteracted by the administration of dantrolene, which raises the calcium requirement for excitation–contraction coupling in skeletal muscle. This may be the reason why dantrolene appears to make a difference in survival for patients presenting with very high body temperatures. Possible reasons for hyperthermia associated with MDMA are summarized in Table 3.

Table 3 Aetiology of hyperthermia associated with MDMA

- Prolonged exertion
- Warm environment

Amphetamine-like effects
- Promotion of repetitive activity (dancing)
- Disregard for body signals (thirst, exhaustion)

Mood-enhancing effects
- Euphoria
- Energy

Serotonin effects
- Increased muscle tone
- Heat production

Secondary effects of hyperthermia
- Increased muscle tone
- Further heat production

Serotonin syndrome

MDMA is one of the many pharmacological triggers of the serotonin syndrome. This syndrome is characterized by a rapid onset, with confusion, diaphoresis, diarrhoea and cardiovascular instability. Increased muscle tone and rigidity are accompanied by shivering, tremor, heightened deep tendon reflexes and myoclonus.[17] The excessive muscle contraction may lead to hyperthermia and death, and this condition has a mortality rate of 10–15%. Serotonin syndrome clearly shows great similarity to the acute hyperthermia and multi-organ failure seen with MDMA toxicity, and also MH and neuroleptic malignant syndrome.[71] An overlap of these conditions seems likely with both being part of the same clinical spectrum. Other drugs known to cause the serotonin syndrome include amphetamines, cocaine and various anti-depressant agents. There is particularly a risk with the combination of MAO inhibitor (MAOI) and any serotonin reuptake inhibitor (SRI). A number of agents commonly used in anaesthesia and critical care also display these characteristics. The phenylpiperidine series opioids, pethidine (meperidine), tramadol, methadone, dextromethorphan and propoxyphene all have a weak SRI effect and linezolid and isoniazid have MAOI properties.[17 47]

The serotonin syndrome may cause severe hyperthermia in MDMA users that have not engaged in significant physical exertion. Mild cases may resolve spontaneously, but should be monitored closely. In severe cases, deep sedation, paralysis and ventilation should be undertaken. As the production of heat is secondary to muscle contraction, and hyperthermia arises because heat production exceeds the body's capacity to lose heat, paralysis immediately cuts heat production and body temperature should decrease rapidly without any further active cooling measures.

Hyponatraemia and cerebral oedema

Awareness of the danger of hyperthermia among users of MDMA led to the practice of drinking large volumes of water to prevent the compounding effect of dehydration. Clubs have been encouraged to provide 'chill-out' areas with free/cheap drinking water available. However, a number of deaths in Ecstasy users have been reported resulting from dilutional hyponatraemia and consequent cerebral oedema.[27 38] Patients generally present with confusion, and convulsions, delirium, or both, and can rapidly progress to coma and death as a result of 'coning' (cerebral oedema, hypoxia and uncal herniation). The practice of drinking large amounts of water, sugared/carbonated drinks, or both, appears to be a major contributory factor. In one case associated with recreational use of MDMA, an elevated level of ADH was reported.[32] In order to examine this phenomenon, Henry and colleagues[29] administered a modest dose of MDMA, 40 mg, to eight healthy volunteers. They showed a marked increase in plasma levels of ADH that would not have been expected at that time of day and were not matched by increases in ACTH (as might be expected if part of a stress response). MDMA thus promotes ADH release in humans. Additionally, as is described above, some genetic polymorphism in relation to COMT may result in a greater release of ADH in some individuals. However, it is clear once again that the circumstances in which the drug is taken affects the incidence of a significant complication, in this case, fluid consumption which exceeds the body's requirements. It is likely that many users who hydrate themselves vigorously would have some degree of hyponatraemia, but only those who consume excessive quantities of fluids achieve clinically significant levels (generally Na <125 mmol litre^{-1}). There may be some benefit if users of MDMA rehydrate with electrolyte-containing fluids.

Conventional management of dilutional hyponatraemia is with fluid restriction, and this is adequate in the great majority of cases of MDMA-associated hyponatraemia. Distinction should be made between the treatment of chronic hyponatraemia and the management of MDMA-associated hyponatraemia, where an acute derangement has occurred. In chronic hyponatraemia, correction should be no faster than 6–8 mmol litre^{-1} per day in order to avoid the osmotic demyelination syndrome.[65] This would be unlikely in the case of an acute hyponatraemia. However, the patient with mild to moderate MDMA-associated hyponatraemia will usually correct automatically by producing a diuresis within hours. The more severely ill patient may not be sufficiently stable to allow such a conservative approach and the use of hypertonic saline solution may be required. There is little evidence concerning the effectiveness of diuretics or mannitol in this situation. In cases of MDMA-related hyponatraemia, other complications may coexist including cardiovascular instability.[24] A more rapid volume correction may be required. Isotonic saline may be most appropriate in this circumstance. Possible reasons for hyponatraemia associated with MDMA are summarized in Table 4.

Table 4 Aetiology of hyponatraemia associated with MDMA

- 'Harm reduction' message to drink fluids

Amphetamine-like effects

- Dry mouth and throat
- Repetitive behaviour—may include compulsively drinking water

Mood-enhancing effect

- Reduced inhibitions and impaired judgement possibly leading to excessive water intake

Serotonergic effects

- Excess ADH production leading to reduced renal response to water load (SIADH)

Liver failure

Hepatic failure has been reported as part of a picture of multi-organ failure attributable to hyperpyrexia. Isolated liver damage of varying severity has also been reported. In the former, liver histology generally shows a picture of centrilobular necrosis and microvascular steatosis, a picture consistent with heatstroke.[42] In isolated liver failure, the histology has been reported to be characteristic of an acute cholestatic hepatitis. The presence of eosinophils and histiocytes constitute strong evidence for a hypersensitivity reaction.[1 13 16] Patients commonly present with jaundice, abdominal pain, raised serum transaminases, hypoglycaemia and elevated prothrombin time. Encephalopathy may occur and presentation can be fulminant. Andreu and colleagues[1] reported that 31% of drug-related hepatotoxicity was attributable to MDMA, second only to that after anti-tuberculous chemotherapy. It represented 20% of all liver failure and 36% of non-viral liver failure in patients <25 yr of age. Treatment is primarily supportive and most patients survive. It is interesting that recurrence has been reported on re-exposure to the drug, which along with the eosinophilic infiltration may suggest an immunologically mediated mechanism.[16] Patients with end-stage liver failure after MDMA use have undergone successful liver transplantation.[1 13]

Acute severe anxiety/panic disorder

Though anxiety is often seen as a minor side-effect of MDMA use, there have been a number of reports of more severe reaction with an acute panic disorder.[40 49 75] This has been reported in subjects without prior personal or family history of an anxiety disorder and where a modest dose of Ecstasy was taken. In one report, another user from the same source reacted similarly[75] though this has not been seen elsewhere. Prior and subsequent Ecstasy use has been reported without similar effect. Though most anxiety and panic reactions settle within hours, there have been reports of a persisting condition lasting several months.[40 49] Benzodiazepines have been found to be acutely effective. Longer-term therapy has been recorded with a

Table 5 The management of acute MDMA toxicity

- Activated charcoal 50 g po ng^{-1} if <1 h post-ingestion

Monitor
- Observe for at least 4 h
- Pulse, blood pressure, ECG, core temperature

Check
- Blood for urea, electrolytes, creatinine, liver function, CPK; consider clotting profile and arterial blood gases
- 12-lead ECG
- Urine drug screen (a positive result for methamphethamine helps to confirm MDMA consumption; specific tests are also available)

Treat
- *Anxiety or agitation*—diazepam (0.1–0.3 mg kg^{-1}) po or i.v.
- *Seizures*—diazepam (0.1–0.3 mg kg^{-1}) i.v. or per rectum (pr)
- *Hyponatraemia*—fluid restrict, consider hypertonic saline if severe
- *Metabolic acidosis*—correct (especially if QT interval prolonged) using sodium bicarbonate
- *Severe hypertension*—consider labetalol
- *Hypotension*—intravascular volume expansion, consider need for central venous access, cardiac output monitoring, etc.
- *Hyperthermia*—simple cooling methods. If temperature >39°C after initial measures, give dantrolene; intubation and ventilation are likely to be required
- *Organ-system failure*—conventional support; promote diuresis of 1–2 ml $kg^{-1}h^{-1}$ with mannitol or furosemide

number of agents including benzodiazepines and SSRI antidepressants.[40 49]

There is good evidence, in a rat model, for a MDMA-induced depletion in central 5-HT levels associated with anxiety and depression, and that this may be in part attenuated by chronic fluoxetine treatment.[21 67] Depression and anxiety have also been reported in human MDMA users. Though there is some diminution after a period of abstinence, the incidence of problems is related to the number of occasions in which MDMA has been used.[43 51] It has been suggested that some users may either be more vulnerable to the effects of MDMA or have pre-existing mental health problems for which they self medicate by using Ecstasy.[70] The possibility of permanent neuronal damage in human users cannot be excluded.

Management of acute MDMA toxicity

A scheme for the management of patients with acute MDMA-related complications (Table 5) has been adapted from the UK National Poisons Information Service guidelines.[69] The use of activated charcoal is recommended up to 1 h post-ingestion. However, it is unlikely that patients would present with serious adverse effects so soon. Urgent fluid replacement is essential in the patient with marked hypotension and tachycardia attributable to intravascular volume depletion.

Labetalol is preferred for the treatment of tachycardia and hypertension secondary to the sympathomimetic effects of MDMA. It has both β- and α-adrenoceptor blocking effects and is available in an i.v. formulation. Beta-blockers used in isolation may be associated with increased hypertension because of the loss of β-mediated vasodilatation. However, i.v. esmolol may be useful as a short half-life makes it rapidly reversible.

It is important to replace fluid losses and thus enable thermoregulation. Paralysis may be required in order to break the cycle of heat generation. Any patient with a significantly impaired level of consciousness, seizures or hyperpyrexia requiring aggressive cooling and dantrolene, should be sedated, the trachea intubated and lungs ventilated.[24] It should be remembered that dantrolene takes some time to dissolve and prepare. Each vial of dantrolene contains 20 mg along with 3 g of mannitol and sodium hydroxide to give a final pH of 9.5 after the addition of 60 ml sterile water. Alkalinization of urine along with an adequate diuresis may protect the kidneys from failure because of myoglobinuria. The mannitol contained with dantrolene may help to promote the desired diuresis of 1–2 ml kg^{-1} h^{-1}, though this may require supplementation.

Patients with hyponatraemia often have a normal or low temperature and should not be given i.v. fluids, as fluid restriction is usually sufficient. In most cases, treatment is essentially supportive. However, temperature control is important and immediate volume replacement followed by dantrolene and aggressive cooling is likely to be useful with severe hyperthermia. It is important to remember that temperature on arrival may not represent the peak and continued monitoring is required. Conversely, the temperature may have already peaked and significant tissue damage occurred before arrival at hospital.

Paralysis and ventilation is the best management for acute serotonin syndrome.

Consideration should be given to the early establishment of invasive monitoring access and a haemodialysis catheter if multi-organ failure and DIC is expected.

Conclusion

It is clear that despite large-scale consumption of MDMA, serious acute illness remains relatively rare. However, when complications occur, they can be life-threatening, and require the implementation of a clearly thought plan, based on the clinical state and knowledge of the physiological effects and toxicity profile of MDMA. There are still many unanswered questions regarding the pathophysiology and pharmacology of the acute toxic effects of MDMA. It is clear that many different neuroendocrine systems can be affected and that the variety of side-effects may depend upon a multitude of other factors both environmental and pharmacogenetic. Additionally, there still remains the possibility of permanent damage to serotonergic neurological pathways in users of MDMA.[10 20 43 44 51 63 68 70]

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